

A comparative study on the neurotoxicity of n-pentane, n-hexane, and n-heptane in the rat

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ABSTRACT The neurotoxicity of n-pentane, n-hexane, and n-heptane have been studied in Wistar strain male rats after exposure to 3000 ppm of n-pentane, n-hexane, or n-heptane for 12 hours a day for 16 weeks. The nerve conduction velocity and the distal latency were measured before the beginning of the exposure and after exposure for four, eight, 12, and 16 weeks. The experiment showed that n-hexane disturbed the conduction velocity of the motor nerve and the mixed nerve and prolonged the distal latency in the rat's tail, but that n-pentane and n-heptane did not. The light and electron microscopic examination showed that the peripheral nerve, the neuromuscular junction, and the muscle fibre of the rats exposed to n-hexane were severely impaired, but those of the rats exposed to n-pentane or n-heptane showed no particular changes even after 16 weeks of exposure. These results show that n-hexane is far more toxic to the peripheral nerve of the rat than n-pentane or n-heptane. It is necessary to study the neurotoxicity of other petroleum hydrocarbons, since some reports suggest that petroleum solvents might possibly contain neurotoxic hydrocarbons other than n-hexane.

For many years petroleum solvents had been considered to be relatively non-toxic, although they were recognised as being fire hazards.^{1,2} One of the main ingredients in many petroleum solvents, n-hexane, was one of those considered to be non-toxic, but recently many cases have been reported of polyneuropathy caused by commercial hexane or by petroleum solvents containing n-hexane.³⁻⁹ Animal experiments have shown that commercial hexane and pure n-hexane could damage the peripheral nerves of mice and rats¹⁰⁻¹³ and also the central nervous system of rats and cats.^{12,14,15} Therefore many cases of polyneuropathy that have occurred in factories where organic solvents were used have been attributed by many researchers to n-hexane. Commercial hexane, however, usually contains not only n-hexane but also its isomers and other hydrocarbons. For example, hexane used in the manufacture of vinyl sandals was found to contain n-hexane, 2-methylpentane, 3-methylpentane, and methylcyclopentane, with n-hexane accounting for about 60% of the total.⁵ Five cases of polyneuropathy have been reported to have been

caused by a petroleum solvent containing 5% hexane, 14% heptane, and 80% pentane in a belt-manufacturing shop.⁷ A petroleum benzene that caused five cases of polyneuropathy in a workshop cleaning silk brocade sash contained C₅ to C₉ hydrocarbons—that is, n-pentane to n-nonane and their isomers—and n-hexane accounted for only 12.3% of the total.⁸ The solvents and glues used in the shoe factories where 20 workers developed polyneuropathy were reported to contain 79%-95% of alkanes including n-pentane, n-hexane, n-heptane, and their isomers.⁹ The results of one animal experiment showed that exposure for five to six months to 1500 ppm technical heptane that did not contain n-hexane damaged the peripheral nerve of the rat as effectively as 2000 ppm of technical hexane.¹⁶ From these reports it is uncertain whether only n-hexane is liable to induce the development of polyneuropathy or whether other petroleum solvents may also have this potential. Petroleum solvents are used in large quantities in industry, usually as mixed solvents consisting of many hydrocarbons. It is important, therefore, from the viewpoint of occupational health to study the relation between the chemical structure and the neurotoxicity of ingredients in petroleum

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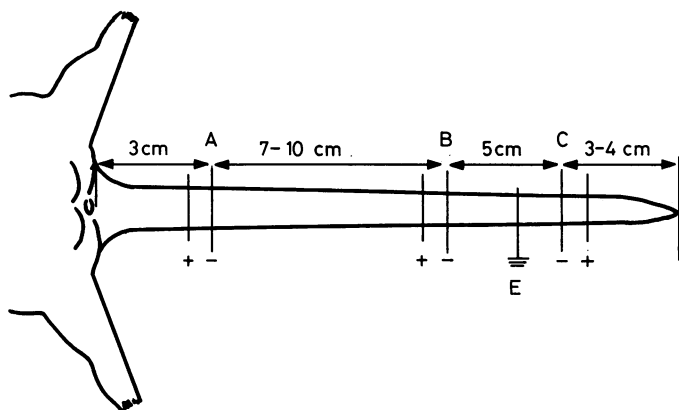


Fig 1 Points of electrodes in rat's tail.

solvents. In the present experiment n-pentane(C_5), n-hexane(C_6), and n-heptane(C_7), major ingredients of many petroleum solvents, were chosen for the comparative study of nerotoxicity.

Method

Twenty-eight Wistar strain male rats (mean body weight 308 g, $SD \pm 18$) were used for the experiment. The rats were divided into four groups of seven, and separate groups were exposed to 3000 ppm of n-pentane, n-hexane, n-heptane, or fresh air in an exposure chamber for 12 hours a day for 16 weeks.¹⁷ These exposure conditions were thought most likely to yield a demonstrable neuropathy at least in the n-hexane group in the light of previous experiments.^{10-12, 18} The temperature and the relative humidity in the chamber fluctuated in the ranges of 23.5-24.5°C and 41-61%. The n-pentane, n-hexane, and n-heptane were more than 99% pure and the concentrations of the vapours in the exposure chamber were measured daily by gas detector and twice weekly by gas liquid chromatography. The measured concentrations were 3080 ± 200 ppm of n-pentane, 3040 ± 270 ppm of n-hexane, and 2960 ± 200 ppm of heptane (mean \pm SD, for 16 weeks).

The conduction velocity of the peripheral nerve was measured in the rat's tail. The rat was wrapped in a towel to keep it immobilised without anaesthesia and laid on its back to allow electrodes to be inserted in the tail at the points shown in fig 1. The electrode was a stainless steel needle, 0.34 mm in diameter and about 15 mm long. After the insertion of the electrodes, the tail was immersed in a paraffin bath with the temperature maintained between 37 and 38°C. The conduction velocity of the tail nerve was measured more than four minutes after immersion, and the measurement was finished within 20 min-

utes of immersion, as in a previous experiment.¹⁹ The tail nerve was stimulated by a square pulse of 0.3 msec duration, 2 c/s and supramaximal strength with an electrostimulator SE-3 with an isolating unit (Nihon Koden); and the biopotentials were observed with an Addscope (ATAC-350, Nihon Koden). One hundred nerve impulses were observed and summated to obtain the following indices: motor nerve conduction velocity (MCV) = AB/latency time (AC-BC); distal latency (DL) = latency time (BC = 5 cm); mixed nerve conduction velocity MNCV (CA) = CA/latency time (CA); MNCV (CB) (distal part) = CB/latency time (CB); MNCV (BA) (proximal part) = BA/latency time (CA-CB).

The body weight, MCV, DL, and MNCV (CA, CB, and BA) were measured before exposure and after four, eight, 12, and 16 weeks of exposure. Two rats exposed to n-hexane and one from each of the other groups were killed after 16 weeks' exposure, and the following organs investigated by light and electron microscopy: the gastrocnemius and soleus muscles, the dorsal trunk of the tail nerve at the proximal and distal portions, and the tibial nerve. Under anaesthesia the rats were perfused from the left ventricle with a fixative that contained paraformaldehyde and glutaraldehyde. Tissue was fixed in the same fixative and then postfixed with osmium tetroxide. After staining en bloc with uranyl acetate, the tissue was dehydrated and embedded in epon. Sections were stained with uranyl acetate and lead citrate, and examined with the electron microscope (HITACHI HU11-DS). For light microscopy, tissue was embedded in paraffin and stained by hemalaun and eosin.

Results

The changes in body weight, MCV, and DL are shown in fig 2. The body weight of the n-pentane

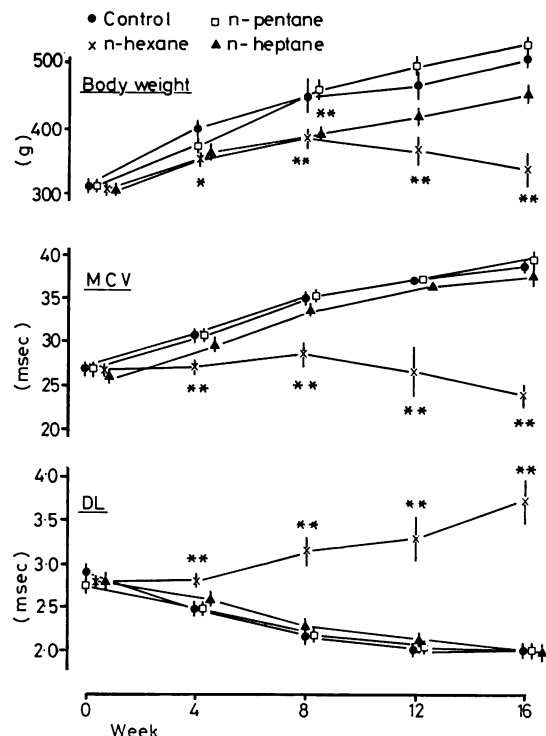


Fig 2 Changes in body weight, motor nerve conduction velocity (MCV) and distal latency (DL) (mean \pm SE). Significance level: * $p < 0.05$, ** $p < 0.01$.

group was slightly less than the controls after four weeks' exposure, but was greater than the controls on and after eight weeks' exposure. These differences were not statistically significant, however. In the n-hexane group the gain in body weight was depressed after four and eight weeks' exposure, and thereafter the actual body weight gradually decreased. In these animals the body weight was significantly less than the controls on and after four weeks' exposure. The gain in body weight was also depressed in the n-heptane group and body weight was significantly lower than the controls after eight weeks' exposure. After this time the weight gradually increased, and there were no statistically significant differences between the n-heptane group and the control after 12 and 16 weeks' exposure.

No abnormal changes were observed in the behaviour of the n-pentane and n-heptane groups or the controls throughout the experiment. An unsteady and waddling gait was observed in one of the seven rats in the n-hexane group after 10 weeks' exposure, and after 12 weeks four of the seven rats in this group had an unsteady, waddling gait and two had foot drop. The two rats with foot drop died one

and three days before the end of the 16-week exposure period. The five surviving rats all showed unsteady, waddling gaits at the end of 16 weeks and two had foot drop. All had muscular atrophy in the legs.

MCVs in the n-pentane and n-heptane groups and in the controls gradually increased as the rats grew; there were no statistically significant differences in the MCVs in these groups. The MCV in the n-hexane group was significantly less than the controls after exposure for four weeks and gradually decreased after eight weeks (fig 2). MCVs could not be measured in two of the rats in the n-hexane group after 16 weeks' exposure because no EMG response appeared at the distal part (C) of the tail.

Distal latencies in the n-pentane and n-heptane groups and in the controls gradually decreased as the rats grew; no statistically significant differences were noted in these groups (fig 2). DL in the n-hexane group was prolonged after four weeks' exposure, and much more so on and after eight weeks' exposure. After 16 weeks of exposure, DL in two of the n-hexane group of rats could not be measured

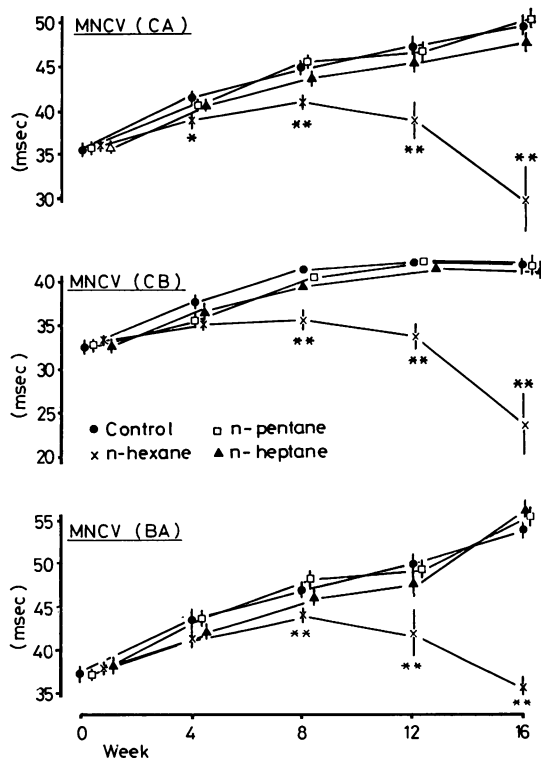


Fig 3 Changes in mixed nerve conduction velocity (MNCV) (mean \pm SE). MNCV (CB): distal part, MNCV (BA): proximal part, BA = CA-CB. Significance level: * $p < 0.05$, ** $p < 0.01$.

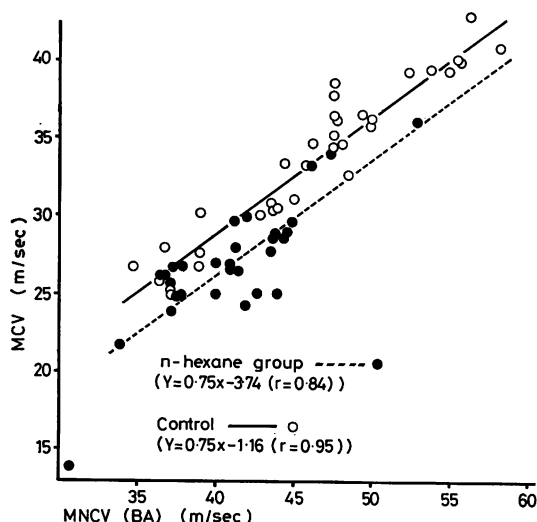


Fig 4 Correlation between MCV and MNCV (BA) in n-hexane group and control.

because no EMG response appeared at the distal part (C) of the tail. Figure 3 shows the changes in MNCVs. MNCVs in the n-pentane and n-heptane groups and in the controls gradually increased as the rats grew; in the n-hexane group MNCV (CA) was significantly less than in the controls after four weeks' exposure. On and after eight weeks' exposure, MNCV (CA), MNCV (CB) (distal part of the tail), and MNCV (BA) (proximal part of the tail) in the n-hexane group were significantly less than in the controls. MNCV in the proximal part (BA) showed a gradual increase until eight weeks' exposure, but MNCV in the distal part (CB) showed almost no increase from four weeks' to eight weeks' exposure and the decrease ratios in MNCV (CB) were larger than those in MNCV (BA) on and after eight weeks' exposure. These results indicate that MNCV in the distal part was more severely impaired than in the proximal part. The MNCV may be considered to

indicate the maximal conduction velocity of the afferent nerve in the rat's tail, as MNCV was faster by about 10 m/sec than MCV in the present experiment.

The relationship between MCV and MNCV (BA) in the n-hexane group and in the controls is shown in fig 4 and indicates that both efferent and afferent nerves are impaired in the n-hexane group.

The morphological changes seen in the peripheral nerves, the neuromuscular junction, and in muscle are shown in figs 5-8. The peripheral nerves, neuromuscular junction, and muscle in the n-hexane group were severely impaired after 16 weeks' exposure, and the tibial nerve and the dorsal trunk of the tail nerve showed remarkable paranodal swellings in the myelinated nerve fibres (fig 5a). Electron microscopic examination found an excessive number of neurofilaments, numerous vesicles, multivesicular bodies, mitochondria, myelin-figures, and dense bodies in various sizes and shapes in the paranodal axoplasm and no neurotubules (fig 5b). On the other hand, the nodal part of the nerve fibre contained many neurotubules arranged in parallel but no abnormal organelles. Many denervated neuromuscular junctions were observed in the muscle of the n-hexane group. In some of these denervated junctions, collagen fibres occupied the cleft in place of the nerve terminal (fig 6). Light microscopic examination showed the muscle fibres of the n-hexane group to be irregular in size and shape; the damaged muscle fibres seemed to have an increased number of nuclei (fig 7). Electron microscopic examination showed that the muscle fibres varied from being almost normal to being severely impaired. The severely impaired muscle fibres showed disordered myofilaments, zig-zagging of the z-band, and numerous invaginations of the plasma membrane (fig 8). The morphological examination did not show abnormal changes in the peripheral nerves, muscle, and neuromuscular junction in the n-pentane and n-heptane groups beyond a slight swelling of the mitochondria and the sarcoplasmic reticulum, and a

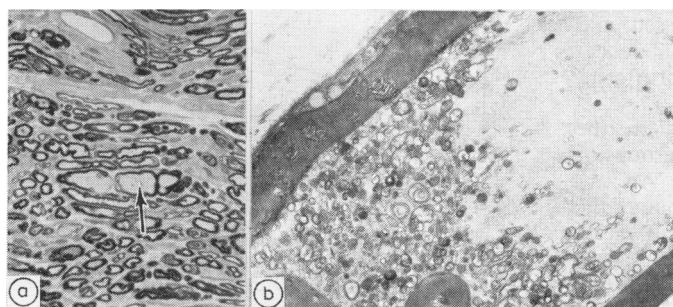


Fig 5 (a) Photomicrograph of an obliquely cut 0.75 μ m epon section stained with toluidin blue. Arrow shows a paranodally swollen myelinated fibre. Tibialis nerve of a n-hexane exposed rat. ($\times 170$.)
(b) Electron micrograph of paranodal swelling of a myelinated fibre. Distal part of tail nerve of n-hexane-exposed rat. ($\times 5000$.)

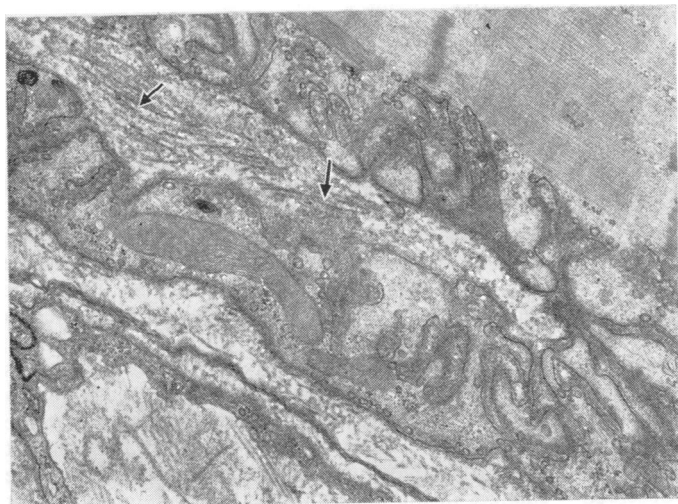


Fig 6 *Electron micrograph of gastrocnemius muscle of n-hexane-exposed rat. Tangentially cut profile of a terminal cleft with secondary folds and vesicles. Arrows show many collagen fibres occupying cleft in place of nerve terminal. ($\times 10\,200$.)*

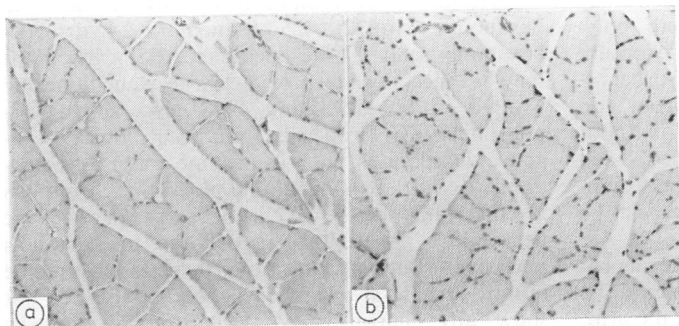


Fig 7 *Photomicrograph of HE-stained cross sections of soleus muscles. (a) control rat, (b) n-hexane-exposed rat. ($\times 190$.)*

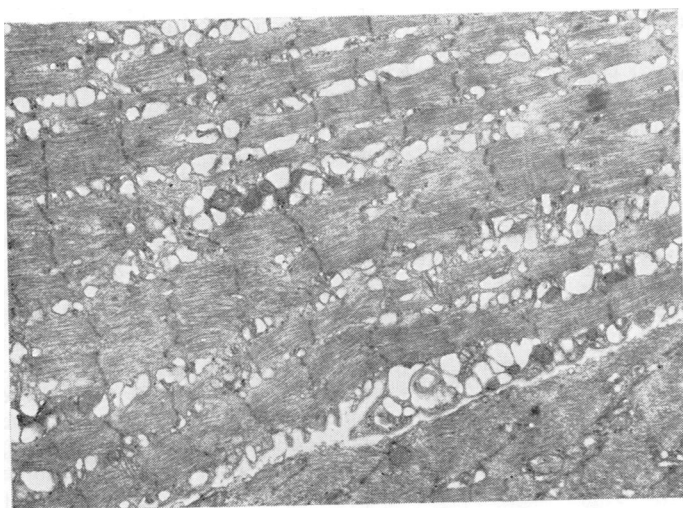


Fig 8 *Electron micrograph of a longitudinal section of gastrocnemius muscle of n-hexane-exposed rat. ($\times 7\,400$.)*

slight dilatation of myofilament bundle that were rarely found in the muscles of both groups.

Discussion

It is well known that the depression of the central nervous system increases as the number of carbon atoms increases in a homologous hydrocarbon series and the same is true in many cases for the gain in body weight. Judging from their physicochemical properties, the effect on body weight might be expected to be in the order n-heptane > n-hexane > n-pentane. But in the present experiment the effect on the body weight gain was in the order n-hexane > n-heptane > n-pentane. n-Hexane has a much more severe effect on body weight than n-heptane and loss of body weight may be one of the important indices of n-hexane intoxication.

Disturbances in gait and foot drop were observed in the rats of the n-hexane group after 10 weeks' exposure. Foot drop has also been reported in rats exposed to 400-600 ppm n-hexane for 24 hours a day after 130 days of exposure.¹² The severe polyneuropathy caused by commercial hexane exposure in man is characterised by severe motor disorders—for example, disturbance in gait, foot drop, and pronounced muscular atrophy with or without sensory impairment. The present experiment showed that severe motor disorders, similar to those seen in workers poisoned with commercial hexane, can be induced in rats by pure n-hexane.

The conduction velocity in n-hexane polyneuropathy in makers of vinyl sandals was reported to be greatly reduced, more so in the leg than in the arm. Even in mildly affected workers with only clinical sensory impairment, there were reductions in MCV, SCV, and EP (MNCV).²⁰ Moreover, a decrease in MCV, SCV, and MNCV and a prolongation in DL was reported in workers with no clinical symptoms and signs but who were exposed to n-hexane.²¹ Thus the reduction in nerve conduction velocity seems to be of great significance in diagnosing n-hexane polyneuropathy, although one report suggests that nerve conduction times are not diagnostic in the workers with polyneuropathy caused by organic solvent containing n-hexane and acetone.⁶ There are only a few reports of nerve conduction velocity in animals exposed to n-hexane.^{16-19,22} The result of the present experiment showed that MCV, DL, and MNCV might detect early impairment of the peripheral nerve in rats exposed to n-hexane. Spencer *et al*¹³ reported a simultaneous, multifocal, apparently random occurrence of giant axonal swellings and accompanying paranodal demyelination and remyelination in rats poisoned by n-hexane,¹³ which implies that nerve conduction velocity is likely to

decrease in the early stages of n-hexane intoxication.

The peripheral nerves of the n-hexane group showed a pronounced axonal degeneration with a relatively slight demyelination similar to that reported by other authors^{12,13,23} but different from the pronounced demyelination and the milder axonal changes observed in advanced human cases of n-hexane polyneuropathy.^{4,24,25} The differences between these observations may be due to the degree and the stage of intoxication, and to the fact that the human cases were exposed to a mixture of organic solvents. The present experiment also showed a pronounced impairment of the motor end-plate, confirming previous reports.^{6,23} Denervated clefts and almost normal end-plates were occasionally found in the same muscle fibre suggesting that the processes of denervation and reinnervation might occur simultaneously in the n-hexane group. The changes in the muscle of the n-hexane group might be attributed mainly to the denervation, but a direct effect of n-hexane on muscle cannot be ruled out.

n-Hexane is metabolised *in vivo* to 2-hexanol, 2-hexanone (MnBK), 2,5-hexanediol, 2-hydroxy-5-hexanone, and 2,5-hexanedione; 2,5-hexanedione may be especially neurotoxic.²⁶ 2,5-Hexanedione and MnBK inhibit CNS and PNS glyceraldehyde-3-phosphate dehydrogenase, but neurologically inactive compounds, such as acetone and 1,6-hexanedione, do not. This metabolic block, which inhibits glycolysis may be the biochemical basis of n-hexane neuropathy.²⁷ n-Heptane is oxidised to heptanols *in vivo*,^{28,29} but rats and monkeys exposed for nine months to 1000 ppm of 2-heptanone did not show any change in MCV,³⁰ although animals exposed to 2-hexanone did develop neuropathy.^{31,32} 2,5-Hexanediol and 2,5-hexanedione also induce peripheral neuropathy in rats but 2-heptanone, 3,5-heptanedione, 2,4-hexanedione, 2,3-hexanedione, 1,6-hexanediol, 1,4-butanediol, glutaraldehyde, and acetone do not.³³ O'Donoghue *et al*³⁴ have tested a series of diketones (2,3-, 2,4-, and 2,5-hexanedione, 2,5-, 2,6-heptanedione and 3,6-octanedione) in the rat, and shown that only γ -diketones (2,5-hexanedione, 2,5-heptanedione, and 3,6-octanedione) are neuropathic. It is not certain whether petroleum solvents containing hydrocarbons other than n-hexane are metabolised to neurotoxic γ -diketones. Truhaut *et al*¹⁶ reported that rats with five or six months' exposure to 1500 ppm technical heptane showed a reduced nerve conduction velocity, an increased refractory period, and a decreased excitability of the sciatic and saphenous nerves as do those exposed to 2000 ppm technical hexane. The heptane used in the experiment contained 52.4% of n-heptane, 16.2% of 3-methylhexane, 9.8% of other heptane isomers, and 21.5% of octane isomers but did not

contain n-hexane.¹⁶ This report suggests that one or more of the hydrocarbons in the technical heptane may be as neurotoxic as n-hexane. It has also been reported that 2,4-pentanedione, which may be one of the metabolites of n-pentane, produced ataxia and disturbances of gait in rats injected for 45 days, despite the MCV remaining normal.³⁵ It seems evident that the neurotoxicity of the hydrocarbons present in petroleum solvents should be studied further.

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